UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/792,176	03/02/2004	Brian T. Chait	016866-000211US	3757

20350 7590 12/22/2006

TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER	
HA, JULIE	
ART UNIT	**PAPER NUMBER**
1654	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/22/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/792,176	CHAIT ET AL.	
	Examiner	Art Unit	
	Julie Ha	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *64-74* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *64-74* is/are rejected.

7)☒ Claim(s) *70* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendment filed on October 31, 2005 is acknowledged. Claims 64-73 are pending in this application.

1. As a result of new grounds for rejection, obviousness Double Patenting rejections are withdrawn. New grounds for rejection follow below.

Objection-Minor Informalities

2. Claim 70 is objected to because of a spelling error. In line 2 of the claim "quadripole" should be corrected to "quadrupole". The Applicants are advised to correct this error.

Rejection- 112, 2nd

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claim 73 recites the limitation "the first set of reaction conditions" and "the second set of reaction conditions" in lines 2 and 3. There is insufficient antecedent basis for this limitation in the claim 72.

Denial of Priority

4. Applicants' claim for domestic priority under 35 U.S.C. 119(e), to Application No. 07/891177, 08/341555 and 09/828326 is acknowledged. The MPEP states that "however, if a claim in a continuation-in-part application recites a feature which was not disclosed or adequately supported by a proper disclosure under 35 U.S.C. 112 in the parent nonprovisional application, but which was first introduced or adequately supported in the continuation-in-part application such a claim is entitled only to the filing date of the continuation-in-part application." See MPEP 201.

The instant application is drawn to claimed method for identifying a covalent modification of an amino acid residue in a polypeptide chain, detecting a mass difference between a formed polypeptide and a modified polypeptide by mass spectrometry, wherein the covalent modification is phosphorylation, acetylation, glycosylation, and a disulfide bond. The Parent applications 07/891177 did not disclose the type of mass spectrometry and the covalent linkages. The parent application 07/891177 did not provide written description, under 35 USC 112, for the type of mass spectrometry and the types of covalent linkages. In the parent application, it is described that the newer mass spectrometry techniques yield useful data, describing MALDI and TOF. However, specifically disclosed mass spectrometry techniques (i.e., ion trap mass spectrometry) are not disclosed in the parent application (see p.4, second paragraph; p 12 and 14). In the parent application, the types of covalent modifications are not provided. The covalent modifications of phosphorylation, glycosylation, acetylation, and disulfide bond do not appear in the parent application. Furthermore,

there is nothing inherent in the parent application about the covalent linkages, phosphorylation, acetylation, glycosylation, and disulfide bonds. As such, the instant Application claims a feature that was not disclosed or adequately supported by a proper disclosure under 35 U.S.C. 112 and priority to the parent application has been denied. **The parent Application does not contain *ipsis verbis* support for the sequences claimed. There is no implicit support since the parent Applications do not provide any specific sequence identifier or provide change with disclosed sequence to arrive at the instant sequences. Accordingly, since the parent applications did not provide sufficient written description for the reasons set forth, the priority to the parent application has been denied. The effective filing date of the Application therefore is June 24, 1996.**

Rejection-35 U.S.C. 112, 1st

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 64, 71 and 72 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of

the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In Regents of the University of California v. Eli Lilly & Co., the court stated:

"A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials. Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606; In re Smythe, 480 F.2d 1376, 1383, 178 USPQ 279, 284-85 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of

certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus. . . ."). Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. The MPEP does state that for generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not define what constitute a sufficient number of representative, the Courts have indicated what do not constitute a representative number species to adequately describe a broad generic. In Gostelli, the Court determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. In re Gostelli, 872 F.2d at 1012, 10 USPQ2d at 1618.

In the instant case, the claims are drawn to a method for identifying a covalent modification of an amino acid residue in a polypeptide chain comprising detecting a mass difference between a formed polypeptide and a modified polypeptide by mass spectrometry. The generic statements modified polypeptide and coupling and terminating reagents do not provide ample written description for the compounds since the claim does not describe a single structural feature. Further, the statements regarding formed and modified polypeptide do not provide ample written description since this only describes the presence of polypeptide. The specification does not clearly define or provide examples of what qualify as compounds of the claimed invention.

As stated earlier, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable claim 64 is a broad generic with respect all possible compounds encompassed by the claims. The possible structural variations are limitless to any class of peptide or a peptide-like molecule. In claim 72, a coupling and terminating reagent is a broad generic with respect to all possible compounds encompassed by the claims. The possible structural variations are limitless to any class of peptide or a peptide-like molecule or organic or inorganic compounds. It must not be forgotten that the MPEP states that if a peptide is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. Here, though the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond compounds disclosed in the examples in the specification. Moreover, the specification lack sufficient variety of species to reflect this variance in the genus since the specification does not provide any examples of derivatives. The specification is void of non-enzymatic modifications of peptides that lead to cyclization of amino-terminal residues, methylation, carboxylation, hydroxylation, and other organic molecules that functions as a peptide-like molecule that qualify for the functional characteristics claimed as a peptide or a peptide-like molecule that can be used for modification of peptides. The specification is limited to covalent modifications that do not belong to the

same class of modifications: glycosylation, phosphorylation, acetylation, and disulfide bonds. The specifications do not describe peptides modified by non-enzymatic modification and other post-translational modifications. Furthermore, it is unclear in the written description how many of these amino acids are covalently modified. For claim 72, the specification is void of any other coupling and terminating agents, such as silane for coupling and chlorotrimethylsilane for terminating reagents. The specification is limited to phenyl isothiocyanate (PITC) and phenyl isocyanate (PIC).

The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Rejection-35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 64-65, 71-74 are rejected under 35 U.S.C. 102 (b) as being anticipated by Chait et al (Science, 1993, 262: 89-92).

The instant claims are drawn to a method for identifying a covalent modification of an amino acid residue in a polypeptide chain comprising detecting a mass difference between a formed polypeptide and a modified polypeptide by mass spectrometry, wherein the covalent modification is phosphorylation and each reaction mixture containing a peptide ladder comprising a series of adjacent polypeptides in which each member of the series differs from the next adjacent member by one amino acid residue, wherein peptide ladders comprises reacting the formed and modified polypeptide with a coupling and terminating reagents, wherein the coupling reagent is PITC and the terminating reagent is PIC, and the formed and modified polypeptide are analyzed simultaneously in a mixture.

Chait et al teach a new approach to protein sequencing consisting two steps: 9i) ladder-generating chemistry, the controlled generation from a polypeptide chain by wet chemistry of a family of sequence-defining peptide fragments, each differing from the next by one amino acid; and (ii) data readout, a one-step readout of the resulting protein sequencing ladder by matrix-assisted laser-desorption mass spectrometry (LDMS). This reads on claims 64 and 71. The method was used to directly locate a phosphoserine residue in a peptide chain (see abstract). This reads on claim 65. The reference further teaches that the protein ladder sequencing principle exemplified by the generation of a set of sequence-determining fragments from an intact peptide chain with controlled

ladder-generating chemistry. A stepwise degradation is carried out with a small amount of terminating agent present in the coupling step. In this case, 5% phenylisocyanate (PIC) was added to the phenylisothiocyanate (PITC). The phenylcarbamyl (PC) peptides formed are stable to the trifluoroacetic acid (TFA) used to cyclized and cleave the terminal amino acid (AA) from the phenylthiocarbamyl (PTC) peptide. Successive cycles of ladder-generating chemistry are performed without intermediate isolation or analysis of release amino acid derivatives. The mixture of PC peptides is read out in one step by matrix-assisted LDMS (see page 89, Figure 1). This reads on claims 64, 71-74.

7. Claims 64, 66, and 70 are rejected under 35 U.S.C. 102(b) as being anticipated by Hunt et al (Biomedical Mass Spectrometry, 1981, 8(9): 397-408).

The claims are drawn to a method for identifying a covalent modification of an amino acid residue in a polypeptide chain comprising detecting a mass difference between a formed polypeptide and a modified polypeptide by quadrupole mass spectrometry, wherein the covalent modifications are acetylation.

Hunt et al teach a new approach to the direct sequencing of oligopeptides in complex mixtures produced by enzymatic and acid hydrolysis of large protein segments and polypeptides in general. Mixtures of oligopeptides containing 2-8 residues are N-acetylated and N, O-permethylated and then volatilized directly into the ion source of a tandem or double analyzer mass spectrometer without fractionation by wet chemical or chromatographic steps (see page 398, left column, lines 3-11). This reads on claim 64 and 66. The instrument employed in the present study is a Finnigan triple quadrupole

mass spectrometer (see page 398, left column, lines 36-37). This meets the limitation of claim 70. Furthermore, oligopeptide mixture analysis by collision-activated dissociation can also be accomplished on the triple quadrupole with Q1, Q2, and Q3 operating in the RF, RF and RF-DC modes (see page 398, right column, lines 29-32). Furthermore, under chemical ionization (CI) conditions when Leu and Ile residues occur at the n-terminus of oligopeptide, the collision activated dissociation mass spectrum of the $[A_1]^+$ sequence ion from Leu-Leu, Ile-Leu, Ile-Ala, and Leu-Ala can be distinguished (see page 405, right column, lines 18-23). This reads on claims 64, 70-71 and 74.

8. Claims 64 and 68 are rejected under 35 U.S.C. 102(b) as being anticipated by Tam JP (US Patent # 5144006).

The instant claims are drawn to a method for identifying a covalent modification of an amino acid residue in a polypeptide chain comprising detecting a mass difference between a formed polypeptide and a modified polypeptide by mass spectrometry, wherein the covalent modification is a disulfide bond.

Tam JP teaches a method for oxidative folding of peptide and protein substrates to form disulfide bonds using dimethyl sulfoxide and other equivalent sulfoxides as mild oxidizing agents. The reference teaches using 20% DMSO in aqueous solution as the oxidative folding reagent, the disulfide formation by the DMSO oxidation was rapid in all model peptides studies. A 50% conversion to the disulfide was found to be effected in about 5 to 30 minutes. This meets the limitation of claim 68. The reaction in was followed by analytical C_{18} reverse-phase HPLC for purification to give 32 to 45% overall yield. The integrity of each purified peptide was determined by Cf-252 fission ion mass

spectrometry and the observed molecular mass was found to agree with the calculated values (see column 4, lines 16-33).

9. Claims 64 and 67 are rejected under 35 U.S.C. 102(b) as being anticipated by Stahl PD (US Patent # 5432260).

The instant claims are drawn to a method for identifying a covalent modification of an amino acid residue in a polypeptide chain comprising detecting a mass difference between a formed polypeptide and a modified polypeptide by mass spectrometry, wherein the covalent modification is phosphorylation is a glycosylation.

Stahl PD teaches the glycopeptides were synthesized in four steps. First, the unmannosylated peptides were made on an ABI peptide synthesizer. The peptides were then purified using reverse-phase and ion-exchange chromatography. Mannose units were then attached via a 2-imino-2-methoxyehtyl thiomannopyranoside. Finally, the mannosylated peptides were purified by reverse-phase and ion-exchange chromatography (see column 9, lines 50-58). This meets the limitation of claim 67. The purified peptides were then analyzed by amino acid analysis and mass spectrometry (see column 10, lines 21-23). Furthermore, identification and characterization of the glycopeptides was through amino acid analysis, mass spectrometry, Dionex carbohydrate chromatography system, and fluorescamine analysis for free amines to verify structure (see column 10, lines 64-68).

Rejection-35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

10. Claims 64 and 69 are rejected under 35 U.S.C. 102(a) as being anticipated by Qin et al (Analytical Chemistry, 1996, 68: 1784-1791).

As described in paragraph 5, the claims are drawn to a method for identifying a covalent modification of an amino acid residue wherein said mass spectrometry is ion trap mass spectrometry.

Qin et al teach a newly configured matrix-assisted laser desorption/ionization ion trap mass spectrometer (MALDI-ITMS) designed for biological applications that require the determination of the primary structures of proteins, e.g., the rapid identification of proteins and the elucidation of posttranslational modifications (e.g., phosphorylation, glycosylation, and disulfide mapping). In particular, mixtures containing as many as 30 peptide components can be rapidly and sensitively analyzed without prior chromatographic separation of the components (see abstract and conclusions). This reads on claims 64 and 69.

Conclusion

11. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Julie Ha whose telephone number is 571-272-5982. The examiner can normally be reached on Mon-Fri, 8:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Julie Ha
Patent Examiner

12/20/10
ANISH GUPTA
PRIMARY EXAMINER